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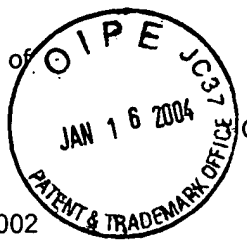
AF 1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER RULE 116
EXPEDITED HANDLING PROCEDURES



In re Patent Application of: Atty Dkt. 2801-18
C# M#

BOTTAZZI et al. Group Art Unit: 1644

Serial No. 09/555,473 Examiner: NOLAN

Filed: February 26, 2002 Date: January 16, 2004

Title: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE & RULE 132 DECLARATION

This is a Response to the Office Action dated October 16, 2003, in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	0.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**0.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Attached: Rule 132 Declaration		**0.00**
TOTAL FEE ENCLOSED	$	**0.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**EXPEDITED HANDLING** **RESPONSE AFTER FINAL REJECTION**
BOTTAZZI et al.	Atty. Ref.: 2801-18
Appl. No. 09/555,473	Group: 1644
Filed: February 26, 2002	Examiner: NOLAN

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * * *

January 16, 2004

Mail Stop AF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE UNDER RULE 116

Responsive to the Official Action dated October 16, 2003, reconsideration and withdrawal of the Section 102 rejection of claims 17-19 over Alles (Blood, Volume 84, No. 10 (November 15), 1994: pages 3483-3493) in view of ATCC Catalog No. 30-2002 is requested in view of the following and the attached Declaration.

Claims 17-19 are pending.

The noted Section 102 rejection is the only outstanding rejection of the claims.

The attached Declaration expresses the beliefs of one of skill in the art that one of ordinary skill in the art would believe that the Alles reference does not teach pharmaceutical compositions or pharmaceutical compositions containing

pharmaceutically acceptable excipients, also containing an active ingredient of the pending claims.

As noted in the attached, the Declarant beleives that one of ordinary skill in the art would not consider DMEM of Alles to be a pharmaceutically acceptable excipient.

One of ordinary skill in the art will appreciate that an "excipient" is "anything other that the drug substance in the dosage form", as noted in the copy of the ICH Harmonised Tripartite Guideline, Stability Testing of New Drugs Substances in Products Q1A R(2), which has been previously filed.

This definition of an "excipient" is confirmed by the copy of Volume 3, No. 3 "Technical Reports" from Albany Molecular Research, Inc. "Definition of Frequently Used Terms and Regulatory Affairs and Quality Assurance" by Steven W. Fordham and Gary M. Klee, copyright 1999, which has been previously filed.

Moreover, page 628 from Butterworths Medical Dictionary Second Edition, McDonald Critchley, Editor–in-Chief, a copy of which has been previously filed with the Examiner, notes under the entry "excipients" that "excipients must not have therapeutic action on their own...".

The Declarant further believes that one of ordinary skill in the art would appreciate that DMEM is not a pharmaceutically acceptable excipient.

DMEM is believed to include the following constituents:

- CaC12 (anhydrous);
- Fe(NO3)3-9H2O;
- MgS04 (anhydrous);
- KCl;
- NaCl;

- NaHC03;
- NaH2P04*H20;
- Choline Chloride;
- Folic Acid;
- myo-Inositol;
- Nicotinamide;
- D-Pantothenic Acid (hemicalcium);
- Pyridoxine-HCl;
- Riboflavin;
- Thiamine-HCl;
- L-Arginine-HCl;
- L-Cystine-2HCl;
- L-Glutamine;
- Glycine;
- L-Histidine-HCl-H2O;
- L-Isoleucine;
- L-Leucine;
- L-Lysine.HCl;
- L-Methionine;
- L-Phenylalanine;
- L-Serine;
- L-Threonine;
- L-Tryptophan;
- L-Tyrosine-2Na-2H2O;
- L-Valine;
- D-Glucose;
- Phenol Red, Sodium Salt; and
- Sodium Pyruvate.

Among the listed constituents of DMEM are the following: Choline Chloride, Folic Acid, Myo-Inositol, Nicotinamide, D-Pantothenic Acid (hemicalcium), Pyridoxine-HCl,Riboflavin, Thiamine-HCl, L-Arginine-HClL-Cystine-2HCl, L-Glutamine, Glicine, L-Histidine-HCl-H2O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, Tyrosine-2Na-2H2O, L-Valine, and Sodium Pyruvate. These components, at least, will be recognized by one of ordinary skill in the art to be drug substances such that the inclusion of the same in

DMEM would lead one of ordinary skill in the art to appreciate that DMEM is not a pharmaceutically acceptable excipient, as the term is generally recognized in the art.

The following previously submitted documents support this conclusion, and further copies of the same should not be required: page 48 of the Merck Manual which describes the use of Nicotinamide (also known as niacinamide) for treating pellagra; page 16611 of the Merck Manual which described the use of folic acid for treating coronary artery disease; excerpt from Merck's website which describes choline chloride as having a lipotropic therapeutic activity; a printout from the International Program on Chemical Safety indicating that choline chloride is a nutrient and dietary supplement with therapeutic uses; a printout from the website "suprahealth.com" indicating that folic acid has a number of therapeutic applications; a printout from the website of "biopsychiatry.com" indicating that myo-inositol has therapeutic capacity and applications; and a printout from Blue Cross also indicates that therapeutic activity of myo-inositol.

The Declarant also states that she believes one of ordinary skill in the art will appreciate that Alles does not provide pharmaceutical compositions and/or pharmaceutically acceptable excipients because, for example, the supernatant of Alles described on page 3485, first full paragraph, of Alles would not be expected to be an administerable pharmaceutical composition. More specifically, the Declarant believes one of ordinary skill in the art will appreciate that it is more likely than not that the solutions of Alles contain, for example, COS cells metabolites, catabolites and residual components of the cellular lysis, such as virus related or released by the DNA of the COS cells. One of ordinary skill in the art would appreciate therefore that even if DMEM

were a pharmaceutically acceptable excipient, which the Declarant does not believe is reasonable, the Alles document fails to provide pharmaceutical compositions.

The Declarant believes therefore that one of ordinary skill in the art would appreciate that the PTX3 protein described in Alles is dissolved in a solution which, more likely than not, may be toxic and/or infective such that the solution is not a pharmaceutically acceptable excipient and the composition is not adminsterable as a pharmaceutical composition.

Accordingly, one of ordinary skill in the art would believe that Alles fails to teach each and every aspect of the above-quoted patent claims.

Withdrawal of the Section 102 rejection of claims 17-19 is requested along with a Notice of Allowance.

The undersigned requests an interview with the Examiner, prior to issuance of a further Action, if the claims continue to be rejected for any reason after entry and consideration of the above and the attached.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

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Arlington, VA 22201-4714
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al. Atty. Ref.: 2801-18

Serial No. 09/555,473 Group: 1644

Filed: February 26, 2002 Examiner: NOLAN

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * * *

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

I, Rita De Santis, whose professional address is Sigma Tau SpA R&D - Immunology Area Via Pontina, Km 30.400, 00040 Pomezia – Rome, hereby declare:

1) I am presently the Head of Immunology Area at Sigma-Tau SpA - Research and Development, Pomezia, Roma, the assignee of the above-identifled application. A copy of my professional resume is attached.

2) I have reviewed the above-identified application, including the pending claims, Alles (Blood 1994, 84 (10) 8483-8493) (hereinafter "Alles") and ATCC Catalog No. 30-2002.

3) I have been advised that the U.S. Patent Office official in charge of the abov - identified application believes that Alles (Blood, Volume 84, No. 10 (November 15), 1994: pages 3483-3493) provides each and every aspect of the following patent claims:

> "17. An orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing as an active ingredient the amino acid sequence of the long pentraxin PTX3 having sequence SEQ ID NO: 1, and a pharmaceutically acceptable excipient."
> "18. The composition according to claims 17, for the treatment of tumours."
> "19. The composition according to claim 17, for the treatment of diseases caused by bacteria, fungi, protozoa or viruses, in which said bacteria, fungi, protozoa or viruses show the capacity to bind the long pentraxin PTX3."

based on the specific disclosure at page 3485, first full paragraph, wherein I have been advised that the U.S. Patent Office official has summarized this disclosure as teaching "expressing the full-length human PTX3 protein in COS cells and incubated in DMEM and then isolating the protein in the supernatant for Western analyses." I have also been advised that the U.S. Patent Office official in charge of the above-identified application has asserted that "at the point the protein was isolated in the supernatant that had DMEM in it, the claims drawn to a pharmaceutical composition were anticipated." I have been advised that "anticipated" as used by the U.S. Patent Office official means that the official believes that each and every aspect of the above-quoted claims is taught by the Alles reference.

4) I have also been advised that the U.S. Patent Office official believes, generally, that the compositions of Alles are "pharmaceutical" compositions of the above-quoted claims.

5) I believe that one of ordinary skill in the art would believe that the Alles reference does not teach pharmaceutical compositions or pharmaceutical compositions containing pharmaceutically acceptable excipients, also containing an active ingredient of the above-quoted claims.

6) I have also been advised that the U.S. Patent Office official in charge of the above-identified application believes that one of ordinary skill in the art would believe that DMEM of Alles is a "pharmaceutically acceptable excipient".

7) I do not believe that one of ordinary skill in the art would consider DMEM of Alles to be a pharmaceutically acceptable excipient.

8) One of ordinary skill in the art will appreciate that an "excipient" is "anything other that the drug substance in the dosage form", as noted in the copy of the ICH Harmonised Tripartite Guideline, Stability Testing of New Drugs Substances in Products Q1A R(2) which I have been advised has been previously filed with the U.S. Patent Office.

9) This definition of an "excipient" is confirmed by the copy of Volume 3, No. 3 "Technical Reports" from Albany Molecular Research, Inc. "Definition of Frequently Used Terms and Regulatory Affairs and Quality Assurance" by Steven W. Fordham and Gary M. Klee, copyright 1999, which I have been advised has been previously filed with the U.S. Patent Office.

10) Moreover, page 628 from Butterworths Medical Dictionary Second Edition, McDonald Critchley, Editor–in-Chief, a copy of which I have been advised has been previously filed with the U.S. Patent Office, notes under the entry "excipients" that "excipients must not have therapeutic action on their own...".

11) I have been advised that the U.S. Patent Office official in charge of the above-identified application has also relied on ATCC Catalog No. 30-2002 for the description of DMEM and the assertion that the U.S. Patent Office official in charge of the above-identified application has asserted that this ATCC catalog reference indicates that DMEM is "useful as an in vivo solution, thereby meeting the pharmaceutical composition limitation."

12) I believe that one of ordinary skill in the art would appreciate that DMEM is not a pharmaceutically acceptable excipient.

13) It is my understanding that DMEM includes the following constituents:

- CaC12 (anhydrous);
- Fe(NO3)3-9H2O;
- MgS04 (anhydrous);
- KCl;
- NaCl;
- NaHC03;
- NaH2P04*H20;
- Choline Chloride;
- Folic Acid;
- myo-Inositol;
- Nicotinamide;

- D-Pantothenic Acid (hemicalcium);
- Pyridoxine-HCl;
- Riboflavin;
- Thiamine-HCl;
- L-Arginine-HCl;
- L-Cystine-2HCl;
- L-Glutamine;
- Glycine;
- L-Histidine-HCl-H2O;
- L-Isoleucine;
- L-Leucine;
- L-Lysine.HCl;
- L-Methionine;
- L-Phenylalanine;
- L-Serine;
- L-Threonine;
- L-Tryptophan;
- L-Tyrosine-2Na-2H2O;
- L-Valine;
- D-Glucose;
- Phenol Red, Sodium Salt; and
- Sodium Pyruvate.

14) Among the listed constituents of DMEM are the following:

Choline Chloride, Folic Acid, Myo-Inositol, Nicotinamide, D-Pantothenic Acid (hemicalcium), Pyridoxine-HCl,Riboflavin, Thiamine-HCl, L-Arginine-HClL-Cystine-2HCl, L-Glutamine, Glicine, L-Histidine-HCl-H2O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, Tyrosine-2Na-2H2O, L-Valine, Sodium Pyruvate.

15) The components listed above in ¶14) will be recognized by one of ordinary skill in the art to be drug substances such that the inclusion of the same in DMEM would lead one of ordinary skill in the art to appreciate that DMEM is not a pharmaceutically acceptable excipient, as the term is generally recognized in the art.

16) I have been advised that the following documents, which support the statement made in ¶15) above, have been previously submitted to the U.S. Patent Office and that further copies of the same are not required: page 48 of the Merck Manual which describes the use of Nicotinamide (also known as niacinamide) for treating pellagra; page 16611 of the Merck Manual which described the use of folic acid for treating coronary artery disease; excerpt from Merck's website which describes choline chloride as having a lipotropic therapeutic activity; a printout from the International Program on Chemical Safety indicating that choline chloride is a nutrient and dietary supplement with therapeutic uses; a printout from the website "suprahealth.com" indicating that folic acid has a number of therapeutic applications; a printout from the website of "biopsychiatry.com" indicating that myo-inositol has therapeutic capacity and applications; and a printout from Blue Cross also indicates that therapeutic activity of myo-inositol.

17) Beyond the above and indicated previously submitted documents, I believe one of ordinary skill in the art will appreciate that Alles does not provide pharmaceutical compositions and/or pharmaceutically acceptable excipients because, for example, the supernatant of Alles described on page 3485, first full paragraph, of Alles would not be expected to be an administerable pharmaceutical composition. More specifically, I believe one of ordinary skill in the art will appreciate that it is more likely than not that the solutions of Alles contain, for example, COS cells metabolites, catabolites and residual components of the cellular lysis, such as virus related or released by the DNA of the COS cells. One of ordinary skill in the art would appreciate therefore that even if

DMEM were a pharmaceutically acceptable excipient, which I do not believe is reasonable, the Alles document fails to provide pharmaceutical compositions.

18) I believe therefore that one of ordinary skill in the art would appreciate that the PTX3 protein described in Alles is dissolved in a solution which, more likely than not, may be toxic and/or infective such that the solution is not a pharmaceutically acceptable excipient and the composition is not adminsterable as a pharmaceutical composition.

19) Accordingly, I believe that one of ordinary skill in the art would believe that Alles fails to teach each and every aspect of the above-quoted patent claims.

20) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By _____
Rita De Santis

Date: January 8th, 2004